

## REMARKS

Claims 28 and 32 have been amended to better claim the invention. Claim 29 has been canceled without prejudice to avoid redundancy, in view of the incorporation of the limitations of claim 29 into claim 28. Claim 28 correctly recites alkali metal and alkaline earth metal nitrites, as requested by the Examiner. This corrects an obvious, inadvertent clerical error. Claim 28 has also been amended to correctly recite oxides of nitrogen as required by the Examiner. Support is found in this application at page 7, lines 5-8 and in WO 95/22335 at page 3, lines 28-36. Claim 28 has been amended to recite that pH is reduced below 4 at the site of use; support is found in the as-filed claim 7, for example. The recitation of the "said pharmaceutically acceptable acidifying agent and said pharmaceutically acceptable source of nitrite ions are separately disposed for admixture to release oxides of nitrogen at the intended environment of use" is supported in the as-filed application at page 7, lines 5-8 and at page 3, lines 28-36. The recitation of treating bacterial, virus and fungal conditions is supported by priority application PCT/GB95/00338 at page 3, lines 15-16. Claim 32 has been amended for proper dependency and to correct an obvious inadvertent typographical error. None of the amendments made herein constitutes the addition of new matter.

### The Rejection under 35 U.S.C. 112, first paragraph

Claims 28-31 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner has objected to the recitation of "to establish a pH at the environment of use below 4", alleging that reducing the pH and establishing a certain pH are not the same.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 28 to recite "to reduce the pH at an environment of use to below 4". This is supported by original claim 1, for example.

The Rejection under 35 U.S.C. 112, second paragraph

Claim 32 has been rejected under 35 U.S.C. 112, second paragraph, as alleged indefinite for depending from a canceled claim.

In the interest of advancing prosecution, claim 32 has been amended to correctly recite dependency on claim 28 and to correct an obvious inadvertent typographical error (nitrite replaces nitrate).

With the amendments to the claims, Applicants respectfully submit that the claims meet the requirements of Section 112, second paragraph, and the withdrawal of the rejection is respectfully requested.

The Rejection under 35 U.S.C. 102

Claims 28 and 30 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by BIOSIS abstract 1987:466265. Applicants respectfully traverse this rejection.

The cited abstract is said to disclose topical staining with silver nitrate followed by application of 5 or 10% salicylic acid in petrolatum.

Applicants respectfully note that the claims recite nitrite ions. There is no evidence that the abstract discloses any nitrite ions at the site of application of the silver nitrate stain and salicylic acid, and the Office Action appears to be mistaken with respect to the cited abstract teaching nitrite ions. Applicants note that the Specification discusses conversion of nitrate to nitrite by oral bacteria, but the teachings of the cited abstract are limited to the

skin. There is no indication that bacteria capable of converting nitrate to nitrite are present on the skin in the experiments described in this abstract.

In view of the foregoing, the rejection for anticipation is not proper, and it must be withdrawn.

Claims 28-29 and 31 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by the Mardi patent (US 4,595,591). Applicants respectfully traverse this rejection.

Mardi is said to disclose a combination of two vials, the first containing a sodium nitrite solution and the second containing a solution of other components, including nitric acid in a concentration and amount that gives a pH below 1 at the site of use (col. 2, lines 26-37 and col. 5, lines 10-62). The composition is said to be used to treat verruca vulgaris and condyloma accuminatum. The Examiner has alleged that nitrites are released from the reaction of nitric acid and organic acid. The Patent Office concluded that the present invention is anticipated by this reference.

In the interest of advancing prosecution and without acquiescing to the rejection, claim 28 has been amended to recite that the pH at the environment of use is below 4 and that the dosage form does not cause significant inflammation at the site of use, and that the dosage form consists essentially of an organic acid and a source of nitrite ions. Support for the limitation related to inflammation is found at page 3, lines 24-29, and in the priority application (WO 95/22335) at page 2, lines 27-31. Applicants maintain that treatment taught by Mardi is harsher than that of the present claimed invention. In Mardi, the goal of the application of the therapeutic composition is the removal of pathologically altered tissue, and that is achieved by applying the strongly acidic material (pH less than 1) at the site of the altered tissue. The Mardi treatment causes immediate denaturation of the integumental proteins and mummification (fixation) of the anatomical structure (col. 3, line 66 to col. 4, line 2). The tissue is killed at the point of application and there will, as a result of the exposure to strong acid, be significant inflammation surrounding the site of tissue death.

Mardi teaches that the use of strong acids, and thus potentially dangerous nature of the compositions means that the compositions are only to be administered by medical practitioners and not by the patient (see col. 10, lines 14-17). This is in clear contrast from the present claimed composition which does not cause significant inflammation when applied to the skin (see present specification at page 3, lines 24-29). In addition, the present claims specify organic acid. Nitric acid is not an organic acid, and its presence is excluded by the recitation of consisting essentially of.

In view of the foregoing and the amended claims language, Applicants respectfully maintain that the claimed invention is not anticipated by the cited Mardi patent and request the withdrawal of the rejection.

#### The Rejection under 35 U.S.C. 103

Claims 28-31 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Mardi et al. Applicants respectfully traverse this rejection.

Mardi's teachings have been discussed above. Mardi is said to also disclose the use of keratolytic organic acids such as salicylic acid. The Patent Office has further alleged that the same dosage form is explicitly taught by Mardi et al. The use of salicylic acid is also allegedly taught by Mardi.

In the interest of advancing prosecution and without acquiescing to the rejection, claim 28 has been amended to recite that the dosage form consists essentially of a source of nitrite ions and a source of organic acid. This does not encompass the possibility of nitric acid, as set forth in Mardi. The Mardi reference can be properly viewed as teaching away from the present claimed invention in requiring the nitric acid in combination with an organic acid. Furthermore, the tissue browning and tissue destruction after administration and need for a medical practitioner for the application of the Mardi composition clearly indicate that the Mardi composition is very different than that of the present invention, and it could not

have been predicted from the cited art that the milder treatment compositions of the present invention could kill infectious organisms or successfully treat microbial infections.

In view of the amendments to the claims and the arguments provided above, Applicants respectfully maintain that the present claimed invention is not *prima facie* obvious over the cited art, and the rejection should be withdrawn.

#### Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance and early notification thereof is requested.

If, in the interest of expediting prosecution, the Examiner has questions or comments, he is invited to telephone the undersigned at the indicated telephone number.

This Amendment is accompanied by a Petition for Extension of Time and payment of the fee required by 37 C.F.R. 1.17. It is believed that this Amendment does not necessitate further extension of time the payment of any additional fees under 37 C.F.R. 1.16-1.17. If this is incorrect, however, please grant further extension of time as needed and charge any further fees due pursuant to the foregoing Rules to Deposit Account No. 07-1969.

Respectfully submitted,

/donnamferber/

Donna M. Ferber  
Registration No. 33,878  
Customer No. 23713

GREENLEE, WINNER AND SULLIVAN, P.C.  
4875 Pearl East Circle, Suite 200  
Boulder, CO 80301  
Telephone (303) 499-8080  
Facsimile: (303) 499-8089  
Email: winner@greenwin.com  
Attorney Docket No.: 14-06